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EXAMINER	
SINGH, ANOOP KUMAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,168	EGASHIRA, KENSUKE	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6 and 9-19* is/are pending in the application.

4a) Of the above claim(s) *1,5,6 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments to the claims filed May 14, 2008 have been received and entered. Claims 1, 5, 6, 9-10 have been amended, while claims 2-4, 7-8 have been canceled. Applicants have also added claims 11 -19. Currently, claims 1, 5-6, 9-19 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II (claims 9-10) in the reply filed on May 14, 2008 is acknowledged. The traversal is on the grounds that the special technical feature of the invention is a gene eluting stent comprising a gene encoding a hybrid polypeptide comprising a FNCBD and N-terminal deleted MCP-1. Applicants argue that claims 1, 5-6 and 9-15 should be examined together. This is not found persuasive because under PCT Rule 13.2, instant claims lack the same or corresponding special technical features as discussed in previous office action. Briefly, document WO 00/24412 teaches drug/gene leaching stent, while WO2002/14505 discloses gene encoding hybrid polypeptide comprising fibronectin collagen domain linked with either anti inflammatory agent MCP-1 or angiogenic agent. It would have been obvious for one of ordinary skill in the art to substitute VEGF in gene eluting stent disclosed in WO 00/24412 with another gene for delivery encoding hybrid polypeptide comprising fibronectin collagen domain linked with either anti inflammatory agent MCP-1 for the treatment of vascular disorder including stenosis particularly since it was known to one of ordinary skill in the art that anti inflammatory agent such as MCP-1 wherein N-terminal is deleted is critical for treating vascular stenosis (see Egashira Hypertension, 2003; 41, 834-41, IDS). Since there is lack of unity and claimed stent comprising gene encoding a hybrid protein is not a technical feature that defines a contribution over the prior art. The restriction between product and process is proper. Furthermore, MPEP

1893.03(d) states: If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 5-6, 16-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 14, 2008.

Claims 9-15 are under currently under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application 2004-077581, filed in Japan on March 18, 2004. It is noted, however, that applicants have not filed a certified copy of the priority application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing vascular restenosis following thickened endocardial membrane angioplasty in a subject, comprising

administering directly to a injured blood vessel of said subject, a gene eluting stent comprising a surface layer which contains a gene encoding a hybrid polypeptide comprising a fibronectin-derived collagen binding domain (FNCBD) polypeptide and N-terminal deleted monocyte chemoattractant protein-1(MCP-1), wherein vascular restenosis is reduced as compared to placing a stent which does not contain a gene encoding a hybrid polypeptide comprising FNCBD polypeptide and an N-terminal deleted MCP-1 in the blood vessel, does not reasonably provide an enablement for administering numerous types of stents coated with or containing a nucleic acid that encode the fusion polypeptides in numerous blood vessels of the subject or any blood vessel , or the method comprising placing any gene eluting stent for the treatment of plurality of vascular disorder including stenosis caused by post percutaneous transluminal coronary angioplasty (PTCA) or percutaneous transluminal angioplasty (PTA), as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion

of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims are drawn to a method of treating vascular restenosis, acute coronary syndromes or cerebral ischemia, which comprises placing a gene eluting stent comprising a surface layer which contains a gene encoding FNCBD polypeptide and MCP-1. Subsequent claim limit the reduced restenosis comparing restenosis in presence and absence of gene encoding fusion polypeptide of the invention. Newly added claims further limit the structure of stent and wherein gene encoding the hybrid polypeptide comprises sequence set forth in SEQ ID NO: 1. Claims 14 and 15 further limits the method of claim 9 wherein restenosis is relapsed stenosis of post percutaneous transluminal coronary angioplasty (PTCA) or percutaneous transluminal angioplasty (PTA). The instant specification describes certain embodiments of the invention relating to using a drug/gene eluting stent that has a layer containing the gene encoding a hybrid polypeptide on the surface, wherein the hybrid polypeptide is preferably a bound product of a polypeptide of fibronectin-derived collagen binding domain (FNCBD) and an anti-inflammatory factor MCP-1 (see para. 12 and 13 of the published application). The specification embraces the potential of directly delivering the genes encoding a hybrid polypeptide, particularly in uniform microcapsules of hybrid polypeptide, to the lesion that can reduce the given doses (see para. 23 and 24 of the specification). When given their broadest reasonable interpretation, in view of the as filed specification, the claims encompass placing drug/gene eluting stent in any blood vessel for treating restenosis caused by plurality of distinct reasons for restenosis in any subject with or without a restenotic vessel. It is noted that claims read on placing claimed stent prophylactically as well as after PTCA or PTA comprising a nucleic acids that

encode the hybrid protein comprising any FNCBD and ND MCP-1 in any vectors or plasmids, or the method comprising placing the stent of the invention in any vessel.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to identify the subjects or vessels that may have restenosis and further treating or administering prophylactically nucleic acids encoding FNCBD and ND MCP-1 polypeptide into any blood vessels, as claimed in claims 9-15 of the instant application.

The state of the prior art with regard to transfer of genes, using a stents, is effectively summarized by the reference of Duverger et al. (U.S. Patent Publication No.: 20030100889, filed Jul. 3, 2002) and Takahashi et al (Gene Ther. 2003; 10(17):1471-8) that showed vectors encoding marker genes could be utilized to deliver genes to the arterial vascular tissue in rabbit and porcine models of restenosis, together with various stents (Duverger et al. paragraphs (0029-0030), (0034-0035) and Example 1 and 2 and abstract of Takahashi). Duverger et al. further describe the inclusion of genes of interest that may be utilized in their gene transfer technique (paragraph 49, page 4). It is further noted that while percutaneous coronary interventions such as angioplasty, stent placement, or atherectomy may be combined with gene therapy, "More than 50 clinical trials have failed to identify an effective therapy for restenosis...to be effective, this therapy must consider not only the appropriate gene but also a means of optimal local delivery" (page 1, paragraph 3). The breadth of the claims embrace delivering nucleic acid into any blood vessel for gene therapy, the prior art effectively addresses the limitations, drawbacks and unpredictability of said vectors. For example, Thomas et al. (Nature Rev.Genet. 4: 346-358; 2003) describe the failure of gene delivery after clinical trial failed to show efficacy. Thomas et al States "The

stumbling block seemed to be the vehicles that were used to deliver the therapeutic genes to the target tissue; early recombinant viral vectors were inefficient, failed to persist in host cells and transgene expression was typically short lived (column 1, p. 346). It should therefore be noted that expression of any gene of interest encoded by a simple nucleic acid, such as a plasmid or any viral or non viral vector as embraced by the breadth of the claims would be transient and would not allow to treat relapsed stenosis of PTCA and PTA. Thomas et al. further state: "The ability to accurately predict vector-related side effects at a particular dose is confounded in human studies by the degree of variability between immune responses in different individuals". ..."T-cell responses can still be elicited against the expressed transgene product, particularly if the vectors transduce cells. The route of vector administration might affect the degree to which cells are transduced; route of administration has a profound effect on the development of T-cell responses to transgenes that are expressed from certain viral vectors (column 2, p. 353, last two paragraphs). In the instant case, the claims as recited do not require the nucleic acid molecule is part of an expression vector operably linked to any regulatory sequences, such as any promoter that permits the expression of nucleic acid molecule in cells of blood vessel. Given the broadest reasonable interpretation these claims embrace any promoter that would allow the expression of transgene nonspecifically in any cell upon implantation in blood vessel. The specification does not provide guidance on the manufacture and use of any specific vectors comprising nucleic acid encoding fusion polypeptide. It does not provide guidance on the use of naked DNA molecules for treating vascular stenosis that is relapsed stenosis of post percutaneous transluminal coronary angioplasty (PTCA) or percutaneous transluminal angioplasty (PTA). Further, the literature at the time of filing does not provide guidance on how to get RNA polymerase to efficiently prime to a DNA strand that lacks a promoter for sustained period of time for treating vascular restenosis. It is noted that Huang et al (The Journal of Gene Medicine, 2003, 5 900-

908) describe the poor transgene expression after naked plasmid injection in skeletal muscle of heart. It is emphasized that Huang et al show inefficient expression from a CMV based plasmid (abstract) because of possible silencing of the promoter in quiescent skeletal and cardiac myocytes (see page 906, col. 2, last para.). Therefore, the skilled practitioner would be unable to practice the claimed invention in a manner commensurate in scope with the claims for treating any vascular restenosis. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

The specification discloses a stent coated with a gene encoded a marker gene, LacZ, which is indwelled in an iliac artery of a hyperlipemic rabbit loaded with 1% cholesterol for four weeks. The gene expression analysis after three days showed 60-70% of intimal cells and 50% of medial and outer membrane cells expressing the marker gene (Example 2). The specification further teaches stent made from a biodegradable base material containing a plasmid composed of a gene encoding FNCBD-7ND hybrid polypeptide in the same hyperlipemic rabbit model showed reduced microphage infiltration (see figure 2) in gene-coated stent group in comparison with that in the metal stent group. The experiment involved an n number of 5, and included a single time point of 10 days for the measurement of the macrophage infiltration or thickness of endocardial membrane. The examples did not include any additional time points to determine variation in the decreased restenosis. The examples also did not include other gene comprising any FNCBD and ND MCP-1 other then SEQ ID No: 1. The examples did not provide for placing stent through any of the multitude of blood vessels in the subject. As recited claim 9 read on placing gene eluting stent in any subject, the specification or examples also did not include either the identification of a subject or the prophylactic placement of stent to any subject that do not require treatment via any of a multitude of blood vessels.

In view of the lack of teachings or guidance provided by the specification with regard to treatment of restenosis placing stent comprising vectors, plasmids or nucleic acid encoding hybrid polypeptide of the invention, to a subject by placing said stent in any blood vessels, and the lack of teachings or guidance provided by the specification with regard to the amount and time necessary for delivery of the numerous hybrid gene to a subject, , and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Egashira (Presentation at Japanese Society of Gene Therapy Young Investigator Award July, 2003 as appeared in The Journal of Gene Medicine 2005 Dec:7(12):1588-9), Ishikawa et al (WO/2002/14505, dated 02/21/2002, relying on 2004/0053368 for English translation, IDS, hereafter 1) and Ishikawa et al (hereafter 2, WO/2000/049159, dated 8/24/2000) .

It is noted that Examiner has relied on a U.S. published application no. 2004/0053368 as being an English translation of the cited Japanese WO document, while relying solely on the WIPO document for the rejection.

Additionally, although Egashira is published in December 2005, however, the reference is applied as it work was presented in 9th annual meeting held at Tokyo on July, 2003 (see page 1588, col. 1, para. 1).

With respect to claim 9, Egashira et al teach a method of reducing vascular restenosis by placing 7NDMCP-1gene -eluting stents in iliac arteries of hypercholesterolemic rabbits and nonhuman primates. Regarding claims 10, Egashira et al compared stent based delivery of 7ND to control bare stents to determine suppressed monocyte infiltration, MCP-1 expression, and proliferation of cells in the neointima and media (see page 1588, col. 2, last para.). With respect to claim 11, Egashira et al teach applying a primer layer to an exterior surface of the stent wherein polymer is coated containing plasmid forming the gene layer in the base. It is noted that coating a gene on the surface of stent would mean that plasmid is entrapped between the layers of polymer that is coated on the surface of the stent meeting the limitation of the claim. Furthermore, cDNA sequence of 7ND (N-terminus deletion mutant of human MCP-1) was also known to one of ordinary skill at the time of filing of this application as evident from the disclosure (see page 1588, col.2, para.1). Regarding claim 13, Egashira et al disclose anti inflammatory effect with gene eluting stent capable of reducing restenosis (see page 1589, col. 1 and 2). Although, Egashira et al teach all the method step for reducing vascular restenosis but differed from claimed invention by not disclosing a gene encoding hybrid polypeptide comprises FNCBD and ND MCP-1.

However, prior to instant invention, Ishikawa (1) reported gene encoding fibronectin derived collagen binding polypeptide that could be used for drug delivery. It is also reported that the functional polypeptide is ligated to the carboxyl terminal of the collagen-binding domain (see papa 17). Furthermore, Ishikawa (1) also embraced the potential of fusion of the functional polypeptide with the collagen-binding domain having the amino acid sequence of the polypeptide in human fibronectin wherein functional polypeptide included several angiogenic

growth factor and MCP-1 (see para. 59 and 61 of the specification). Although, Ishikawa (1) contemplated FNCBD could be used for drug delivery but did not provide any explicit motivation to include for local delivery of transgene.

The deficiency of Egashira and Ishikawa (1) is cured by Ishikawa (2), who provide guidance with respect to topical retention and prolonged, controlled slow release of the physiologically active polypeptide by providing a biomaterial (a physiologically active polypeptide/collagen composite) produced by combining the collagen-binding physiologically active polypeptide as described by Ishikawa (1) with a polypeptide from collagen (see page 14, lines 1-10, and page 88, lines 1-10). Ishikawa (2) reported that a collagen-binding physiologically active polypeptide which is provided with both the activity of the physiologically active peptide and the collagen- binding activity can be produced by ligating the collagen-binding domain of fibronectin (FN) with the physiologically active peptide by genetic engineering means. In addition, Ishikawa (2) reported the sequence (SEQ ID NO: 8) for FNBCD that has 100% homology with residue 1-1023 of SEQ IDNO: 1).

Accordingly, in view of the teachings of Egashira, Ishikawa (1) and Ishikawa (2), it would have been obvious for one of ordinary skill in the art, at the time the claimed invention to modify the method of Egashira by substituting gene encoding 7NDMCP-1 in -eluting stents with a hybrid polypeptide comprising a FN-CBD polypeptide and an 7ND-MCP-1to improve the local gene expression. One of ordinary skill in the art would be motivated to substitute nucleic acid encoding 7ND with a nucleic acid encoding a hybrid polypeptide of FNCBD and 7ND with reasonable expectation of success in achieving the predictable results as the Artisan was well aware of the required structures, the results of physiologically active polypeptide/collagen composite, and prolonged local expression of the gene. It is noted that while Applicant's specific sequences (SEQ ID NO:1) are not specifically taught, there is nothing in the art to demonstrate that the artisan would not expect them to work, and the sequences fall into the general requirements for FNCBD as

disclosed by Ishikawa (2) and Egashira. Hence, it would appear that Applicant's contribution to the art is simply to claim sequences obvious, but not specifically obvious, to the Artisan at the time of invention. Furthermore, KSR has already stated that motivation need not be specific, and only in the case of an infinite number of variants is a specific variant non-obvious. Given that one of ordinary skill in the art was well aware of the results of gene encoding hybrid polypeptide comprising FNBCD and 7ND, the requirements for fusion polypeptide, and was already able to make hybrid polypeptide (FNBCD-EGF) that showed prolonged local expression at the time of invention. Hence, it is prima facie obvious to one the artisan to substitute 7ND with a nucleic acid encoding hybrid polypeptide comprising a FNBCD and 7ND as per the teachings of Egashira, Ishikawa (1) and Ishikawa to obtain prolonged expression of MCP-1 from gene eluting stent as disclosed in the instant application. One who would practiced the invention would have had reasonable expectation of success because that method and required sequence to make gene encoding hybrid polypeptide and its mechanisms were already known in the art in an obvious manner to produce prolonged local expression of transgene. Thus, it would have only required routine experimentation to modify the method of Egashira to include a gene encoding hybrid polypeptide (FNBCD-7ND) in the gene eluting stent to reduce vascular restenosis as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palasis et al (WO/2001/074413, dated 10/11/2001, IDS), Egashira (Hypertension. 2003 Mar;41(3 Pt 2):834-41. Epub 2002 Dec 30, IDS), Ishikawa et al (WO/2002/14505, dated 02/21/2002, relying on 2004/0053368 for English

translation, IDS, hereafter 1) and Ishikawa et al (hereafter 2, WO/2000/049159, dated 8/24/2000).

Palasis et al teach a method of reducing restenosis in a subject, preferably a mammal, by administering to the subject, at a predetermined site in the body, the medical device of the invention wherein administration is to a site of mechanical injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty (see page 4, lines 19-24). It is noted that Palasis et al disclose that the medical device is a metallic stent (see page 4, line 13) that has a biocompatible structure comprises a biocompatible polymeric coating that coats at least a portion of the structure and carries a genetic material (see page 4, line 2). Furthermore, it is disclosed that the medical device (stent) may comprise a carrier comprising a naked nucleic acid molecule (claims 4 and 5). Palasis et al exemplified placing a gene eluting stent in to the intravascular region of subject to reduce restenosis (See example 1 and 6). It is noted that Palasis et al contemplated placing stent in subject that have failed PTCA or acute myocardial infarction (AMI) or abrupt thrombotic closure of the targeted artery (see page 17, lines 10-14). The coating of the stent is performed by immersing a metallic stent in gelatin solution containing crosslinker for 10 seconds, then air drying and controlling the thickness of the coating to about 5-10 mm (see example 1). Although, Palasis embraced the potential of delivering gene eluting stent for reducing restenosis by placing the stent in blood vessel but differed from claimed invention by not disclosing the effect by delivering a gene encoding hybrid polypeptide comprising FNCBD and ND MCP-1.

Egashira cure the deficiency of Palasis by disclosing that inflammatory responses to arterial injury causes continuous recruitment and activation of monocytes mainly through activation of the monocyte chemoattractant protein-1 (MCP-1) pathway resulting in restenosis and atherogenesis (abstract). Egashira reported the sequence of an N-terminal deletion mutant of MCP-1, called 7ND, which lacks the N-terminal amino acids 2 to 8, forms inactive heterodimers with

wild-type MCP-1 (see figure 1A). Additionally, Egashira teaches blockade of MCP-1 by 7ND gene transfer suppressed monocyte infiltration/activation at the injured site and markedly inhibited restenotic changes after balloon injury of the carotid artery in rats and monkeys (See figure 5A and B). In hypercholesterolemic rabbits and monkeys, 7ND gene transfer inhibited monocyte infiltration/activation in the stented arterial wall and thus reduced the development of in-stent restenosis (see figure 5C). Although, Egashira et al teaches a method for reducing vascular restenosis by gene transfer, but differed from claimed invention by not disclosing a gene encoding hybrid polypeptide comprising FNCBD and ND MCP-1.

However, prior to instant invention, Ishikawa (1) reported gene encoding fibronectin derived collagen binding polypeptide that could be used for drug delivery. It is also reported that the functional polypeptide is ligated to the carboxyl terminal of the collagen-binding domain (see papa 17). Furthermore, Ishikawa (1) also embraced the potential of fusion of the functional polypeptide with the collagen-binding domain having the amino acid sequence of the polypeptide in human fibronectin wherein functional polypeptide included several angiogenic growth factor and MCP-1 (see para. 59 and 61 of the specification). Although, Ishikawa (1) contemplated FNCBD could be used for drug delivery but did not provide any explicit motivation to include for local delivery of transgene.

The deficiency of Palasis, Egashira and Ishikawa (1) is cured by Ishikawa (2), who provide guidance with respect to topical retention and prolonged, controlled slow release of the physiologically active polypeptide by providing a biomaterial (a physiologically active polypeptide/collagen composite) produced by combining the collagen-binding physiologically active polypeptide as described by Ishikawa (1) with a polypeptide from collagen (see page 14, lines 1-10, and page 88, lines 1-10). Ishikawa (2) reported that a collagen-binding physiologically active polypeptide which is provided with both the activity of the physiologically active peptide and the collagen- binding activity can be produced by ligating the collagen-binding domain

of fibronectin (FN) with the physiologically active peptide by genetic engineering means. In addition, Ishikawa (2) reported the sequence (SEQ ID NO: 8) for FNBCD that has 100% homology with residue 1-1023 of SEQ IDNO: 1).

Accordingly, in view of the teachings of Palasis, Egashira, Ishikawa (1) and Ishikawa (2), it would have been obvious for one of ordinary skill in the art, at the time the claimed invention to modify the method of Palasis et to include gene encoding 7ND in gene eluting stents to transfer 7ND at the site of injury in blood vessel to reduce restenosis. One of ordinary skill in the art would be motivated to transfer 7ND via gene eluting stent since it was recognized that inflammatory responses to arterial injury causes continuous recruitment and activation of monocytes mainly through activation of the monocyte chemoattractant protein-1 (MCP-1) pathway that results in restenosis and blockage of MCP-1 by 7ND gene transfer would suppress monocyte infiltration/activation thereby reducing the restenosis. Furthermore, using a gene encoding hybrid polypeptide comprising FNCBD and 7ND would also be obvious to one of ordinary skill in the art as the Artisan was well aware of the required structures, advantage of using the gene encoding hybrid polypeptide comprising FNCBD and 7ND in sustained local expression of the gene, the results of physiologically active polypeptide/collagen composite. It is noted that while Applicant's specific sequences (SEQ ID NO:1) are not specifically taught, there is nothing in the art to demonstrate that the artisan would not expect them to work, and the sequences fall into the general requirements for FNCBD as disclosed by Ishikawa (2) and Egashira. Hence, it would appear that Applicant's contribution to the art is simply to claim sequences obvious, but not specifically obvious, to the Artisan at the time of invention. Furthermore, KSR has already stated that motivation need not be specific, and only in the case of an infinite number of variants is a specific variant non-obvious. Given that one of ordinary skill in the art was well aware of the required structures of FNCBD and 7ND, results of gene encoding hybrid polypeptide comprising FNBCD

and 7ND, and was already able to make other hybrid polypeptide (FNBCD-EGF) that showed prolonged local expression at the time of invention. Hence, it is prima facie obvious to one the artisan to express gene encoding a hybrid polypeptide comprising a FNBCD and N-terminal deleted MCP-1 as per the teachings of Egashira, Ishikawa (1) and Ishikawa to obtain prolonged expression of MCP-1 from gene eluting stent of Palasis. One who would practiced the invention would have had reasonable expectation of success because that method and required sequence to make gene encoding hybrid polypeptide and its mechanisms were already known in the art in an obvious manner to produce prolonged local expression of transgene. Thus, it would have only required routine experimentation to modify the method of Palasis to transfer a fusion gene encoding FNCBD and 7ND via gene eluting stent to reduce vascular restenosis as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
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/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632